REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-3, 5-6 and 27-40 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry. Here, independent claim 1 is limited to the embodiments of claims 3-4 and independent claim 39 is limited to the subject being affected by Alzheimer's disease (see claim 2). Entry of the claim amendments is requested because they will reduce the issues on appeal (i.e., the Section 102 rejections as discussed below).

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 3, 5 and 39 were rejected as allegedly anticipated by Shi et al. (J. Clin. Invest. 98:1979-1990, 1996). Applicant traverses because Shi teaches neither culturing endothelial cells from a subject prior to determining whether there is inappropriate sensecence and/or defective angiogenesis (see claim 1), nor assaying for vascular dysfunction in a subject affected by Alzheimer's disease (see claim 39).

Claims 1-3 and 6 were rejected as allegedly anticipated by Kalaria et al. (Ann. N.Y. Acad. Sci. 826:263-271, 1997). Applicant traverses because Kalaria does not teach culturing endothelial cells from a subject prior to determining whether there is inappropriate sensecence and/or defective angiogenesis (see claim 1).

The cited documents do not anticipate the claimed invention because they do not disclose all limitations of independent claim 1 or 39. Moreover, those claims depending from the independent claims are also not anticipated by any document because their limitations are also incorporated in claims depending therefrom. See *In re McCarn*, 101 USPQ 411, 413 (C.C.P.A. 1954).

Withdrawal of the Section 102 rejections is requested because the cited documents fail to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 1396. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-6 and 27-40 were rejected under Section 103(a) as allegedly unpatentable over Grammas et al. (Dementia 6:126-130, 1995) in view of Mulliken et al. (Surgery 92:348-353, 1982). Applicant traverses.

Grammas discloses the effects of amyloid fractions from an Alzheimer disease patient's brain on normal endothelial cells cultured from rat brains. The cited document focuses on the popular hypothesis that pathology lies in the amyloid protein instead of

the discovery represented by Applicant's invention, which is based on endothelial cells having one or more intrinsic defects that would be the cause of vascular dysfunction in a human subject affected by a neurodegenerative disorder or another cognitive impairment. In neither Grammas nor Mulliken are dysfunctional cells from a human subject assayed directly or after culturing. As admitted in the Office Action at page 5, "Mulliken does not teach obtaining endothelial tissue from patients with neurodegenerative disease or another cognitive impairments" (emphasis added).

Even assuming for the sake of argument that "[i]t would have been obvious to one of ordinary skill in the art to modify the methods of Grammas to include the step of culturing the human endothelial cells, as taught by Mullliken, with a reasonable expectation of success" (the Office Action at page 5), the modification asserted by the Examiner would not result in Applicant's claimed invention. Here, the claimed method assays for vascular dysfunction in endothelium or endothelial cells obtained from a human subject affected by a neurodegenerative disorder or another cognitive impairment such as Alzheimer's disease. There would have been no reason to assay such endothelium or endothelial cells for vascular dysfunction because the cited documents focus on toxic effects of Aβ peptide instead of the present invention's focus on intrinsic endothelial cell dysfunction. In contrast, the prior art would have used endothelium or endothelial cells from a normal human subject to avoid having to separate the effects of Aβ peptide on the cell in a subject affected by Alzheimer's disease *before* and *after* it was obtained from the subject. A reasonable expectation of success is also lacking because the prior art does not establish that the defect in Alzheimer's disease is intrinsic to the endothelium or endothelial cells of an affected subject. The popular hypothesis represented by Grammas is that the defect is centered on Aβ peptide that is extrinsic to cells. Applicant submits that these features of their claimed invention are sufficient to distinguish over the cited documents so any other incorrect allegations about their disclosures are not disputed here, but the opportunity to dispute them in the future is reserved.

Therefore, the combination of Grammas and Mulliken does not render obvious the claimed invention because all limitations of the independent claims are not fairly taught or suggested in the cited documents. Moreover, claims depending from those

independent claims are also not made obvious by the documents because their limitations are incorporated in the dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Withdrawal of the Section 103 rejection is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicant submits that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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